Suberoylanilide Hydroxamic Acid (Vorinostat) Up-regulates Progranulin Transcription: RATIONAL THERAPEUTIC APPROACH TO FRONTOTEMPORAL DEMENTIA.

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Authors: Basar Cenik, Chantelle F Sephton, Colleen M Dewey, Xunde Xian, Shuguang Wei, Kimberley Yu, Wenze Niu, Giovanni Coppola, Sarah E Coughlin, Suzee E Lee, Daniel R Dries, Sandra Almeida, Daniel H Geschwind, Fen-Biao Gao, Bruce L Miller, Robert V Jr Farese, Bruce A Posner, Gang Yu, Joachim Herz

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Public Summary:
Progranulin (GRN) haploinsufficiency is a frequent cause of familial frontotemporal dementia, a currently untreatable progressive neurodegenerative disease. By chemical library screening, we identified suberoylanilide hydroxamic acid (SAHA), a Food and Drug Administration-approved histone deacetylase inhibitor, as an enhancer of GRN expression. SAHA dose-dependently increased GRN mRNA and protein levels in cultured cells and restored near-normal GRN expression in haploinsufficient cells from human subjects. Although elevation of secreted progranulin levels through a post-transcriptional mechanism has recently been reported, this is, to the best of our knowledge, the first report of a small molecule enhancer of progranulin transcription. SAHA has demonstrated therapeutic potential in other neurodegenerative diseases and thus holds promise as a first generation drug for the prevention and treatment of frontotemporal dementia.

Scientific Abstract:
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